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Case Report

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A case report of relapsed/refractory primary central nervous system lymphoma

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ABSTRACT

Primary central nervous system lymphoma is a rare and aggressive subtype of non-Hodgkin lymphoma. The disease presents with neurologic findings at the time of diagnosis and responds rapidly to first-line chemo-radiotherapy but frequent and early relapses are observed. Because of the blood-brain barrier, many drugs cannot pass into the central nervous system, limiting effective treatment options. We will try to discuss a relapsed-refractory primary central nervous system lymphoma that exhausted many treatment options

Keywords: Primary central nervous system lymphoma, diffuse large B cell lymphoma, medical and radiation therapy

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare aggressive non-Hodgkin's lymphoma outside the lymph nodes. Currently, high-dose chemotherapy based on methotrexate (MTX) is the standard induction treatment for newly diagnosed PCNSL but effective treatment of relapsed/refractory and elderly PCNSL is still unclear. With the advancement of clinical trials, new drugs and combination therapies such as rituximab and ibrutinib are constantly emerging, increasing the remission rate of resistant and relapsed patients.[1] In this case report, we will try to present a case of relapsed/refractory primary central nervous system lymphoma.

CASE

A 42-year-old male patient, was diagnosed with PCNSL in 2019. (the patient's mass was in the right frontal, radiologic image was compatible with central nervous system (CNS) lymphoma but biopsy was performed and the diagnosis was confirmed because the mass was also suitable for definitive diagnosis). The patient went into remission with high dose and cytarabine(2,000 mg/m^2 every 12 hours total of 4 doses) + radiotherapy (RT) (44 Gy) and started to be followed up. In 2020, the patient whose disease relapsed was given a high-dose methotreaxte-based regimen received an autologous hematopoietic stem cell yerine hematopoietic stem cell transplant. The patient in remission was followed up without treatment until 2022. In November 2022, off-label ibrutinib was approved and ibrutinib was started for the patient who relapsed again. The patient initially responded to ibrutinib and progression in the lesion was detected on magnetic resonance imaging (MRI) after an increase in central nervous system complaints in the 3rd month of treatment. Since the patient had previously responded to a high-dose MTX regimen and more than 2 years had passed since then, temozolamide+high-dose MTX+rituximab regimen was started in January 2023. After the first course of treatment, the patient's right frontal mass significantly decreased in size and symptoms significantly decreased and the same regimen was continued. While the patient was receiving the 4th course, central nervous system complaints developed again and MRI revealed new lesion in the left parietal region and near the hypothalamus and lesion in the old frontal region. The patient who was bradycardic due to edema + mass was first given anti-edema treatment with dexamethasone+mannitol. The patient with partial reduction in complaints was investigated for ongoing clinical trial. He was wanted to be included in the epcoritamab study but was not eligible for inclusion due to age and neurologic side effects. The dose of RT the patient had received previously was calculated. The necrosis dose was not reached. The patient, who had previously benefited from cytarabine treatment and more than 2 years after the end of treatment, was given cytarabine and RT again. Necrosis dose was not reached in RT. The patient benefited significantly

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with the first course of cytarabine+RT. After the 3rd course of cytarabine, the patient's complaints increased again. After MRI revealed an enlarged mass, rituximab+lenalidomide was started with off-label consent. In the 2nd cycle, the patient's symptoms increased and his mass progressed and he died before completing the 2nd cycle.

DISCUSSION

PCNSL is a rare subtype of aggressive non-Hodgkin's lymphoma located in the brain, leptomeninges, spinal cord, cerebrospinal fluid or vitreoretinal compartment without overt systemic disease.[2] It accounts for less than 3% of all cases of non-Hodgkin's lymphoma and almost 3% of all primary central nervous system tumors.[2] Symptoms may start as focal neurologic deficits, personality changes, nausea and vomiting due to increased intracranial pressure. The patient should be rapidly evaluated and then CNS imaging is required.[3] Contrast-enhanced brain MRI is the best imaging option to evaluate patients with PCNSL.[4] Our case; a 42-year-old male patient, was admitted to the neurology outpatient clinic in 2019 with neurological findings at the time of the first diagnosis and it was observed that there was a 5 cm mass in the right parietal lobe on the contrast-enhanced cranial MRI and he was referred to the neurosurgery department and the diagnosis was made by biopsy. Age and performance status (PS) are important prognostic factors but some other details such as comorbidity, organ function, frailty and risk of neurotoxicity should also be taken into account when choosing treatment.[3] Modern treatment of PCNSL includes two phases: induction and consolidation. High dose MTX-based regimens and autologous hematopoietic stem cell transplantation in appropriate patients form the basis of treatment.[4] Whole brain RT is an alternative to autologous hematopoietic stem cell transplantation in case of failure of hematopoietic stem cell harvesting or complications during induction.[3] In our case, cytarabine followed by high-dose MTX-based regimens with induction chemotherapy and RT were administered and autologous hematopoietic stem cell transplantation was performed. Following indication and consolidation treatments, the disease relapsed or developed resistance to treatment in approximately half of the patients.[5] In addition, the presence of the blood-brain barrier prevents polypharmacy in PCNSL.[2] A standard of care for patients with relapsing or refractory PCNSL has not yet been established. Clinical trials should be the preferred treatment option as this is the best strategy to identify new active drugs and strategies that can then be investigated as part of first-line treatment.[4] In the case of late relapse (>24 months) and prior response to high dose-MTX-based regimens, reintroduction of high dose-MTX is a safe and effective strategy.[3] Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, can cross the blood-brain barrier. Rapid and impressive responses have been achieved in CNS lymphoma patients when given as a single agent or in combination.[3,6] Immunomodulatory drugs (lenalidomide and pomalidomide) have been investigated in patients with recurrent or refractory PCNSL, achieving an objective response in half of patients but the response was usually short-lived.[7] Our patient, who went into remission and relapsed approximately 26 months later. MRI revealed involvement in the right fronto-tempo-occipital and left occipital regions consistent with PCNSL (Figure). It was first started on ibrutinib and a response was obtained but when the disease progressed, first a high-dose MTX-based regimen + RT was started, then high-dose cytarabine was given when the disease progressed. When no suitable clinical trial was found, the patient was started on rituximab+lenalidomide. Anti-CD19 chimeric antigen receptor (CAR)-T cells have recently been approved for the treatment of relapsed/refractory diffuse large B cell lymphoma(DLBCL) and have shown promising results in other B-cell lymphomas. This approach deserves to be evaluated in patients with relapsed or refractory PCNSL, given the encouraging preliminary results reported in patients with secondary CNS DLBCL.[8] In our case, the CAR-T treatment option could not be reached and the patient who did not respond to rituximab-Lenalidomide treatment died.

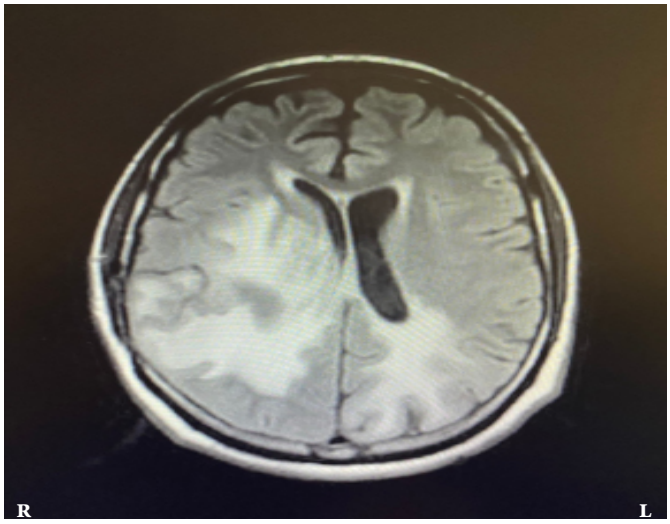

Figure. Right fronto-tempo-occipital involvement on MRI, left occipital appearance compatible with PCNSL
MRI: Magnetic resonance imaging,
PCNSL: Primary central nervous system lymphoma

CONCLUSION

In the treatment of PCNSL, the disease responds to treatment, but relapses occur frequently. The need for new treatment options for patients who have exhausted current treatment options and are progressing/refractory remains current.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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